

Research Protocol on Selective Endovascular Patching of Cerebral Aneurysm Neck Orifices

By Teodoro A. Tigno Jr., M.D.

Koebbe et al in 2006 depicted the evolving practice paradigm on the treatment of cerebral aneurysms shifting from the open craniotomy approach towards endovascular treatment since 2000.[1] In the 15-year period of endovascular neurosurgical growth since the availability of the Guglielmi detachable coil despite its broader initial support[2], various authors have documented suboptimal aneurysmal sac occlusions and postcoiling recurrences with figures ranging from 21.3% for small aneurysms to 50.6% for large aneurysms as well as 52.3% of wide-neck aneurysms versus 23.7% of postcoiled aneurysms with small neck size.[3] [4]. Large aneurysmal remnants were found by the same authors in 27% of examined cases immediately postcoiling, increased remnant size by angiography in 19.1% of 131 postcoiled cases, 14.5% of which required aneurysm recoiling. Thromboembolic events and vessel stenosis postcoiling were also reported [5-12] Despite these reports impetus on the further clinical use of endovascular procedures for aneurysms persisted with the International Subarachnoid Aneurysm Trial which established Level 1 evidence showing a significant reduction in disability or death with endovascular treatment compared with surgical clipping[13]. Broader support for the endovascular alternative continue to be driven by the successive availability of newer stents and stent techniques, coils(bioactive, three-dimensional, ultraoft)and coil placement techniques[14-35] as well as thrombogenic materials[18, 33, 36]. Consequently, intraprocedural complications using the endovascular alternative continue as well to be documented and review of cases of particular subset of aneurysms (MCA, broad-necked, fusiform) restate the need to adequately reconstruct the aneurysmal neck defect enabling a definitive treatment for aneurysms when approached intraluminally [3, 4, 37-66].

The application of magnetic field on biological tissues has been carried out in studies by several authors[67-76]. In 1959, Waller et.al. identified the hemoglobin content of older circulating erythrocytes to contain greater amounts of methemoglobin than young cells (more than 8% observed)[68]. Melville et. al. in 1975[76] using this observation was able to develop the technique of high gradient magnetic separation (HGMS) to initially remove erythrocytes from whole blood. Owen in 1978 contributed refinements to this technique by oxidizing endogenous hemoglobin iron from ferrous to the paramagnetic ferric state(Fe^{+2}) (methemoglobin) using a Na nitrite- phosphate buffer saline (PBS). Knowing that untreated cells, having >95% ferrohemoglobin, are diamagnetic since FeHgbO_2 liganded to molecular oxygen has no magnetic moment, the selective physical retention of paramagnetic cells in a wire matrix was thus demonstrated. The possibility of cell lysis upon entrapment, which can trigger a cascade of deleterious effects on the arterial wall, is an important consideration in vascular remodeling. [69] Iacob et al further showed the HGMS technique allow rbc concentration without apparent destructive effects on the cell[77]. Recent evidence[78-80] indicates that the artery is not only a destination but also a source of mesenchymal stem cells that engraft other tissues needing repair. Porcine coronary smooth muscle (PCSM) cells have been shown to exhibit a

synthetic proliferative phenotype (ON cells) under standard culturing conditions which can be reverted to a contractile phenotype (OFF cells) in a serum-free medium [78]. This phenotypic plasticity of vascular smooth muscle (VSM) cells suggests that PCSM cells provides a useful model in endovascular reconstruction of the arterial wall defect found in aneurysms. Wang et al [80] had also shown that the possible detrimental effects of stent implantation injury and/or balloon overstretch may be attenuated by the administration of Peroxisome proliferators activated receptor –gamma (PPAR-gamma). In a recent finding, Pislaru et al. [70] proved the retention of blood-derived endothelial cells applying magnetic stents intravascularly. The development of an endovascular strategy for the reconstruction of the aneurysmal neck defect using stents as a tissue scaffold, a directed magnetic field, with the incorporation of chemotactic and tissue culture medium in the interlattices of the stent facing the aneurysmal neck orifice thus finds solid basis in literature.

Objectives, Hypothesis and Methodology: This proposal aims to reconstruct the aneurysmal neck defect in the porcine model through an endovascular approach. The hypothetical assumption to be tested in this study is that a directed magnetic field can confine an induced autoimmune response in the intravascular environment. Towards this goal, the following minor objectives are to be achieved in 2 Phases:

Phase I

- (a) To review of the current literature on tissue engineering with respect to the immunological, biochemical and biophysical events occurring with endovascular manipulation.
- (b) To demonstrate the biophysical and rheological laws prevailing upon application of the endovascular strategy for aneurysm neck reconstruction. This would be achieved through:
 - (i) *in vitro* induction of an auto-immune response simulating the endovascular strategy for aneurysmal neck reconstruction with and without application of a directed magnetic field.
 - (ii) *in vivo* endovascular patching of the aneurysmal neck orifice in pig models with previous stent-induced and angiographically demonstrated aneurysms, followed by serial post-patching angiography

Phase II

To establish the applicability of endovascular strategy for reconstructing aneurysmal neck orifices in the porcine model to serve as a basis for future clinical studies in humans. This is to be carried out through:

- (a) Endovascular patching of the aneurysmal neck orifices in 60 pig models with previous stent-induced and angiographically demonstrated aneurysms, 30 of which will be subjected to magnetic field exposure directed to the area of aneurysmal neck defect reconstruction (Group A) versus (Group B) without magnetic field exposure
- (b) Serial post-patching angiography
- (c) Postmortem histopathological comparative studies of Groups A and B 3 months after endovascular patching

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